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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,336	EBNER ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0407,0204*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 24–39 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC §§ 101, 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 24–39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that:

> Applicants respectfully disagree with the Examiner's assertion that Applicants have not disclosed any properties for the protein other than the sequence. Applicants direct the Examiner's attention to the present specification, at, e.g., pages 63-64 where CTGF-3 expression data is presented. Further, page 6, paragraphs 0020-0021 in conjunction with Figures 2 and 3, present comparative analysis with CTGF-1 (Figure 2), as well as an analysis of the CTGF-3 structure in terms of antigenic regions, alpha, beta, turn, and coil regions, amphipathic regions, flexible regions, and hydrophilicity and hydrophobicity regions (Figure 3). Clearly, Applicants have characterized CTGF-3 beyond its nucleotide and amino acid sequence.

Applicants' arguments have been fully considered but they are not persuasive. Figure 3 shows an analysis of the CTGF-3 amino acid sequence. There is no description of the chemical, physical, or biological properties for the protein beyond this analysis of the amino acid sequence. The specification does not disclose a specific biological role of CTGF-3 or its significance. Rather than setting a de minimus standard, § 101 requires a utility that is "substantial", i.e., one

that provides a specific benefit in currently available form. The amino acid sequence analysis and expression data do not provide a specific benefit in currently available form. No assertions of utility are made in the specification regarding the expression data at pages 63-64.

Applicants argue that:

> With respect to the issue of using amino acid homology as a predictor of protein function, Applicants respectfully disagree with the Examiner's interpretation of Henikoff et al. The passages cited by the Examiner relate to the potential difficulties in creating taxonomical classifications of gene family members but do not refute the contention that members within a given gene family (based on amino acid sequence homology) tend to have homologous functions.

Applicants' arguments have been fully considered but they are not persuasive. Although Henikoff indicates that sequence similarity is a precisely defined metric for establishing relatedness, Henikoff does not indicate that sequence similarity of a protein of unknown function to a protein that may have an in vivo function is predictive of, or an assurance of, preserved ultimate function of the related molecule of unknown function. It is noted that the instant specification fails to correlate a specific function of CTGF-3 with any given module of CTGF-3, or even with the entire protein.

Applicants argue that:

> The Examiner also states that "Grotendorst does not ascribe a biological role, function or activity based on the structural relatedness" of members of the CCN family. Paper No. 20070103, p. 5. Applicants note that even if it was true that this particular paper (Grotendorst, Cytokine Growth Factor Rev. 8:171-9 (1997)) does not make activity predictions based on structural relatedness, this fact does not establish that such predictions would not be credible to an artisan in the field. In fact, in another paper Grotendorst does make predictions about members of the CCN family based on their structural relatedness. Grotendorst and Duncan, FASEB J. 19:729-38 (2005) (IDS Document AR18). Further, these predictions are consistent with utilities disclosed in the present application, as will be discussed below in section C.

Applicants' arguments have been fully considered but they are not persuasive. As indicated in the last Office action, Grotendorst (Cytokine Growth Factor Rev. 8:171-9 (1997)) teaches that most of the members of the CCN family lack a clear biological activity and does not ascribe a biological role, function, or activity to CNN family members based on their structural relatedness. Applicants propose ascribing a utility to CTGF-3 based upon its homology with CTGF-1. CTGF-3 is about 44% identical and about 59% similar to human CTGF-1 (Specification, page 7, lines 27-30). However, Zhang (Mol Cell Biol. 1998 Oct;18(10):6131-41) discloses a protein, rCop-1, that is ~70% identical to CTGF-3 (SEQ ID NO: 2), as indicated in the last Office action. rCop-1 represents a new class of CCN family proteins that have functions opposing those of the previously identified members. Thus, the evidence shows that a person of skill in the art would not know how to use CTGF-3 based merely on its identification as a member of the CNN family or its homology to CTGF-1.

Applicants make no attempt to point to any specific section in Grotendorst (FASEB J. 2005 May;19(7):729-38.) wherein "Grotendorst does make predictions about members of the CCN family based on their structural relatedness." In any case, Grotendorst was published in 2005 and is not evidence of what would be considered credible by a person of ordinary skill in the art at the time of applicants' invention. Therefore, Grotendorst (2005) is not probative of the applicant's assertions regarding the proposed utility of CTGF-3 based upon its homology with CTGF-1.

Applicants argue that:

> The present specification fully and clearly sets forth utility for the claimed invention.
>
> For example, Applicants have asserted that the claimed invention is useful in the diagnosis and prognosis of various connective tissue related disorders where there is

significantly altered expression of CTGF-3. See, Specification, p. 31, paragraph 0082. Within the specification, non-limiting examples of diseases or conditions caused by, associated with, or characterized by an over- or under- growth of connective tissue cells are set forth, including cancer, arthritis, fibrosis, atherosclerosis, and osteoporosis. See, id. Indeed, the present specification teaches that increased levels of CTGF-3 can be detected in body fluids or tissues from mammals with cancer, fibrosis, arthritis, or atherosclerosis. In particular, the specification states:

> Thus, the invention provides a diagnostic method useful during diagnosis of connective-tissue related disorders, such as cancer, fibrosis, arthritis, or artherosclerosis, which involves assaying the expression level of the gene encoding the connective tissue growth factor-3 protein in mammalian cells or body fluid and comparing the gene expression level with a standard connective tissue growth factor-3 gene expression level, whereby an increase in the gene expression level over the standard is indicative of these diseases.

Specification, p. 31, paragraph 0083.

The utility of the claimed invention for the detection of cancer in particular is also asserted in the specification at page 33, paragraph 0089: "The present invention is useful for detecting cancer in mammals. In particular, the invention is useful during diagnosis of the following types of cancers in mammals: breast, ovarian, cervical, prostate, bone, liver, lung, pancreatic, and splenic."

The specification further discloses that where a connective tissue related disorder has already been diagnosed according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced CTGF-3 gene expression will experience a worse clinical outcome relative to patients expressing the gene at a lower level. See, Specification, p. 31, paragraph 0084.

In addition, therapeutic uses for the CTGF-3 protein, as well as antibodies to the CTGF-3 protein, are asserted in the specification, including the treatment of individuals who are in need of an increased or decreased level of CTGF-3. See, Specification, pp. 41-48.

It is evident that Applicants have specifically asserted utilities for the claimed invention relating to the detection and treatment of a variety of connective-tissue related disorders associated with an excess or deficiency of CTGF-3 activity. Cancer, fibrosis and fibrotic conditions are connective-tissue related disorders that are explicitly named. Specification, p. 45, paragraph 0129. Indeed, as will be discussed below, experimental results by other groups support the asserted role of CTGF-3 in cancer and in fibrosis.

Applicants direct the Examiner's attention to and request consideration of the following documents which provide experimental support for Applicants' originally asserted utility of CTGF-3 in the diagnosis, prognosis, and/or treatment of cancer (although, as will be discussed, they utilized nomenclature different than "CTGF-3"): WO 98/58063 (IDS Document AN1); WO 99/14327 (IDS Document AO1); WO 99/21998 (IDS Document AP1); Pennica et al., Proc. Natl. Acad. Sci. USA 95:14717-14722 (1998) (IDS Document AR7); Saxena et al., Mol. Cell. Biochem. 228:99-104 (2001) (IDS Document AR15); Zoubine et al., Biochem. Biophys. Res. Comm. 282:421-425 (2001) (IDS Document AS15); Inadera et al., Biochem. Biophys. Res. Comm. 275:108-114 (2000) (IDS Document AS14); and Inadera et al., Biochem. Biophys. Res. Comm. 294:602-608 (2002) (IDS Document AT14); or in the diagnosis, prognosis, and/or treatment of connective tissue-related diseases such as fibrosis and fibrotic conditions: Grotendorst and Duncan, FASEB J. 19:729-38 (2005) (newly cited, IDS Document AR18) and Leask and Abraham, J. Cell. Sci. 119:4803-10 (December 2006) (newly cited, IDS Document AS17).

A nucleotide sequence and corresponding protein identical to CTGF-3, designated GRFLP, is disclosed in AN1. In AN1, it states: "GRFLP is expressed in various libraries derived from cancerous tissues. Therefore, GRFLP appears to play a role in cancer and connective tissue disorders, particularly disorders in which GRFLP is overexpressed." AN1, page 22, lines 28-30.

A nucleotide sequence and corresponding protein identical to CTGF-3, designated PRO261, is disclosed in AO1. In AO1, it was demonstrated that the gene encoding PRO261 was amplified in (1) primary lung tumors, (2) primary colon tumors, (3) colon tumor cell lines, and (4) breast tumor cell lines, relative to normal tissues. AO1, page 70, lines 16-34.

In both AP1 and Pennica et al., the nucleotide sequence and corresponding protein identical to CTGF-3, is designated WISP-2. The following results are presented, supporting a utility for CTGF-3 in the diagnosis, prognosis, and treatment of cancer. First, these two documents demonstrate that the gene encoding WISP-2 is localized to a region on chromosome 20q12 that is a frequent site of DNA amplification in human breast and colon cancers. See, AP1, page 58, lines 25-28, and Pennica et al., page 14720, column 2, paragraph 1. Second, as in AO1, it is demonstrated in AP1 that the gene encoding WISP-2 was amplified in (1) primary lung tumors, (2) primary colon tumors, (3) colon tumor cell lines, and (4) breast tumor cell lines, relative to normal tissues. See, AP1, page 87, line 27, to page 88, line 3. Third, in AP1, it is shown through in situ hybridization that there is particularly strong WISP-2 expression in benign fibroblast-like cells adjacent to infiltrating breast carcinoma cells. See id., page 93, lines 3-17. Finally, in Pennica et al., it is shown through quantitative PCR that the copy number of the gene encoding WISP-2 was increased 2-4 fold in 92% of human colon tumors studied. See, Pennica et al., at page 14720, right column, 3rd full paragraph. Interestingly, however, despite DNA amplification of WISP-2, mRNA expression was reduced in the majority of

colon tumors. Id., page 14722, left column, first full paragraph. Pennica et al. concludes that "[t]he amplification and altered expression patterns of the WISPs in human colon tumors may indicate an important role for these genes in tumor development." Id., last paragraph.

Saxena et al., using differential display, RT-PCR, and DNA sequencing analyses in normal human mammary epithelial cells MEC) and various breast tumor cell lines including MCF-7, ZR-75, T-47D and SKBR2, demonstrated that WISP-2 genes (corresponding to "CTGF-3") are differentially transcribed in normal and breast tumor cells. WISP-2 mRNA transcription was significantly higher in all 4 tumor derived cell lines, but mRNA expression was undetected or minimally detected in normal breast epithelial cells. Saxena et al., page 103, right column. The Saxena Abstract concludes: "The mRNA expression profiles of WISP genes in normal breast epithelial cells and breast tumor derived cell lines indicated a strong possibility of the involvement of WISP-signaling in the development of human breast tumors, and can be utilized as genetic markers of this disease." Zoubine et al. demonstrates that WISP-2 expression was undetectable, or minimally detectable, in normal human mammary epithelial cells, but was overexpressed in MCF-7 breast cancer cells. Expression of WISP-2 in MCF-7 cells was modulated by serum and correlated with the serum-induced MCF-7 tumor cell proliferation, suggesting that WISP-2 is serum responsive and may be a positive regulator of tumor cell proliferation. See, Zoubine et al., Abstract, and page 425, last paragraph.

Inadera et al. (2000) presents results on WISP-2 in connection with their search for novel estrogen-responsive genes. Serial analysis of gene expression (SAGE) for estrogen-treated MCF-7 human breast cancer cells was performed. SAGE analysis of 31,000 and 30,856 tags from non-treated and 17 beta-estradiol ~2)-treated cells for 24 hours, respectively, facilitated the identification of 15,037 different transcripts. Comparison of these two SAGE libraries indicated a remarkable similarity in expression profiles. Among the identified transcripts, four genes were found to be markedly increased for E2-treated cells compared with control cells. Three of the transcripts were known estrogen-inducible genes. The fourth gene was WISP-2, which the authors state has recently been reported as an up-regulated gene in the mammary epithelial cell line C57 MG transformed by the Wnt-1 oncogene. See, Inadera et al. (2000) Abstract. The increase in WISP-2 mRNA was completely prevented by co-incubation with a pure anti-estrogen ICI 182,780, but not by coincubation with cycloheximide, indicating that WISP-2 is directly regulated by the estrogen receptor. The WISP-2 gene was also induced by treating with environmental estrogens. This study represents the first comprehensive gene expression analysis of estrogen-treated human breast cancer cells. Thus, WISP-2 was identified as a novel estrogen responsive gene in human breast cancer cells and this effect is directly regulated by an estrogen receptor. Id., page 114, last paragraph.

In a subsequent paper, Inadera et al. (2002) examined whether WISP-2 could be utilized as a marker for screening environmentally relevant compounds for estrogenicity. In MCF-7 cells, progesterone, dexamethasone, tri-iodothyronine, and 2,3,7,8-

tetrachlorodibenzo-p-dioxin did not regulate the expression of WISP-2, indicating that its induction is highly specific for hormones that interact with the estrogen receptor. Western blot analysis detected WISP-2 protein induced by 17-beta-estradiol (E2), not only in the cell lysates but also in the culture supernatant of exposed cells, indicating that WISP-2 was a secreted protein. The induction of WISP-2 protein by E2 in the culture supernatant was dose-dependent with estimated EC(50) levels between 10 and 100 pM. These results demonstrated the capacity to screen environmental compounds for estrogenicity via WISP-2 induction.

In a more recent paper, Grotendorst and Duncan characterized the CTGF-1 domains and localized two connective-tissue promoting activities to the two halves of the protein. AR18 (published in 2005), abstract. For example, they determined that the myofibrobroblast differentiation and collagen synthesis activity of CTGF-1 lies in the N-terminal domain. Id. They also state that "[t]he high degree of sequence conservation in the various CCN family members suggests a commonality of function in these different gene products." Id., p. 731, col. 2 (emphasis added). Specifically regarding CTGF-3 (Cop-I/Wisp-2), they state "[b]ased on the CTGF data presented here, it would be predicted that these peptides could only act as differentiation-inducing factors and would be incapable of stimulating proliferation." Id., p. 735, col. 2 and p. 737, col. 1. Since the differentiation- and collagen synthesis- inducing activity of CTGF-1 is one of its key activities in regulating connective tissue formation, id., p. 736, col. 2, this prediction in AR18 that CTGF-3 has similar activity to the N-terminal domain of CTGF-1 is consistent with the connective tissue-related utilities disclosed by Applicants for CTGF-3. See also, AS17 (published in December 2006), p. 4803 ("CCN family members..; are overexpressed in pathological conditions that affect connective tissues, including scarring, fibrosis and cancer." (emphasis added)).

Clearly, the numerous publications discussed above support and substantiate Applicants' assertion of CTGF-3's utility in the diagnosis, prognosis, and/or treatment of connective tissue-related diseases such as cancer, and in particular, human breast cancer, and fibrosis. The fact that artisans, as recently as 2005 and December 2006, continue to support Applicants' asserted utilities should reassure the Examiner of the credibility and accuracy of these utilities.

Regarding the specificity of an asserted use, Applicants note that the Utility Guidelines define "specific utility" as a utility that

> is specific to the subject matter claimed and can "provide a well-defined and particular benefit to the public." This contrasts with a general utility that would be applicable to the broad class of the invention .... A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

M.P.E.P. § 2107.01 (I)(A) at 2100-22 to 2100-23 (citations omitted).

Applicants assert that the specification does not provide "[a] general statement of diagnostic utility, such as diagnosing an unspecified disease." Rather, in view of Applicants' assertions in the specification that CTGF-3 is useful in the diagnosis of cancer, coupled with the fact that the CTGF-3 gene was consistently found to be overexpressed in human breast cancer cells and that artisans, as recently as 2005 and December 2006, predicted that CCN family members including CTGF-3 have activity important in connective-tissue formation (thus confirming and supporting Applicants' assertions), Applicants submit that the claimed invention possesses diagnostic and/or prognostic utility in a specified disease state, Le., cancer, such as breast cancer, and fibrosis. Accordingly, since there is "a disclosure of what condition can be diagnosed," it follows that the statement of diagnostic/prognostic utility is clearly sufficient under the Utility Guidelines.

Applicants also note that the Utility Guidelines define "substantial utility" as a utility that

> defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities... An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring.

M.P.E.P. § 2107.01 (I)(B) at 2100-23.

As noted above, Applicants have asserted that CTGF-3 can be overexpressed in cancer and other connective-tissue related conditions (Specification, page 31, paragraph 0083), and have disclosed assays that measure the presence of CTGF-3 in a biological sample (i.d., paragraphs 0086-0098). Thus, not only would such assays have utility in diagnosing connective-tissue related conditions such as cancer and fibrosis, but also in further monitoring clinical outcome, i.e., in prognosis. Clearly, these are substantial "real world" utilities. Thus, similar to the "specific" prong, Applicants' asserted utility therefore clearly satisfies the "substantial" prong of the Utility Guidelines.

Regarding the credibility of an asserted utility, the Utility Guidelines provide as follows:

> Where an applicant has specifically asserted that an invention has particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided).

M.P.E.P. § 2107.02 (III)(B) at 2100-31. In other words, the Examiner "must provide evidence sufficient to show that the statement of asserted utility would be considered

'false' by a person of ordinary skill in the art." M.P.E.P. § 2107.02 (III)(A) at 2100-31. Applicants respectfully submit that the Examiner has not met this burden.

Applicants re-emphasize that they need only make one credible assertion of specific utility for the claimed invention to satisfy the utility requirements, and that once the claimed invention has been found to be useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes indicated in the specification as possibly useful. See, Carl Zeiss Stiftung v. Renishaw plc, 20 U.S.P.Q.2d 1094, 1100 (Fed. Cir. 1991); In re Gottlieb, 140 U.S.P.Q. 665, 668 (CCPA 1964); M.P.E.P. § 2107.02 (I) at 2100-37.

Applicants have asserted in the specification that the claimed invention can be used in the diagnosis, prognosis, or treatment of connective tissues related conditions such as cancer and fibrosis, and have provided "evidence" in the form of publications to substantiate these assertions and provide evidence as to the accuracy, i.e., credibility, of these assertions. Thus, Applicants submit that the above assertions are not only specific and substantial, but credible as well, i.e., the assertion is at least believable to, and would not be considered false by, a person of ordinary skill in the art. The Examiner has not provided any evidence showing that one of ordinary skill in the art would reasonably doubt these asserted utilities. Thus, a prima facie case of lack of utility has not been established.

In view of the above, Applicants assert that the utilities assigned to the claimed invention are specific, substantial and credible. Even assuming, arguendo, the Examiner had established a prima facie showing that the claimed invention lacks utility, Applicants respectfully submit that the numerous publications cited herewith (i.e., the evidence of record) would be sufficient to lead one skilled in the art to conclude that the asserted utility would not be considered "false" by a person of ordinary skill in the art, and therefore would be sufficient to rebut the Examiner's showing. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

Applicants' arguments have been fully considered but they are not persuasive. The specification does not provide any guidance on which cancers, among the laundry list of different cancers recited in the specification, overexpress CTGF-3. This information is critical because, without it, the person of ordinary skill in the art could not have determined, without additional research, which of the disclosed cancers would overexpress CTGF-3. A substantial

utility requires that an invention is useful to the public in its current form, rather than potentially useful in the future after further research.

Hillman (WO 98/58063) has been considered. However, Grotendorst (Cytokine Growth Factor Rev. 8:171-9 (1997)) teaches that most of the members of the CCN family lack a clear biological activity and does not ascribe a biological role, function, or activity to CNN family members based on their structural relatedness. Thus, Grotendorst (1997) indicates that CTGF-3's specific activity could not be reasonably inferred from its characterization as CNN family member. As indicated previously, the specification does not describe the chemical, physical, or biological properties for CTGF-3 beyond Figure 3's analysis of the amino acid sequence. Without knowledge of CTGF-3's specific activity, a skilled worker would not have known whether increasing or decreasing CTGF-3 levels would have been useful for treating disorders "in which GRFLP is overexpressed" (Hillman (WO 98/58063)).

Although Botstein (WO 99/14327) indicates that the gene encoding PRO261 was amplified in (1) primary lung tumors, (2) primary colon tumors, (3) colon tumor cell lines, and (4) breast tumor cell lines, the present specification does not provide any information regarding amplification of the gene encoding CTGF-3.

Botstein (WO 99/21998) has been considered. However, applicants do not explain how placement of WISP-2 in band 20q12-20q13.1 and the frequent site of DNA amplification in human breast cancer in human chromosome 20q12 would lead to the conclusion that CTGF-3 would have utility in the diagnosis, prognosis, and/or treatment of cancer. Botstein also shows expression of human WISP-2 RNA in mesenchymal cells involved in tissue repair and/or collagen deposition. However, its expression was negative on benign and malignant epithelial

cells. Further, this expression is not specific to cancer because it also occurs in benign, inflammatory conditions. Page 93, full paragraph 2. Further, most of the members of the CCN family lack a clear biological activity (Grotendorst (Cytokine Growth Factor Rev. 8:171-9 (1997))). Therefore, the role of CTGF-3 in cancer and in fibrosis has not been established. Therefore, Botstein (WO 99/21998) does not provide evidence that supports a utility for CTGF-3 in the diagnosis, prognosis, and treatment of cancer.

Pennica (Proc Natl Acad Sci U S A. 1998 Dec 8;95(25):14717-22) has been considered. However, applicants do not explain how linkage of WISP-2 to the marker SHGC-33922 (lod = 1,000) on chromosome 20q12–20q13.1 would lead to the conclusion that CTGF-3 would have utility in the diagnosis, prognosis, and/or treatment of cancer. Furthermore, the present specification does not provide any information regarding amplification of the gene encoding CTGF-3 or its up-regulation by Wnt-1. As noted by applicants, Pennica discloses that WISP-2's DNA was amplified, but RNA expression was reduced in the majority of the tumors. However, the present specification teaches that an increase in the CTGF-3 gene expression is indicative of cancer (page 31, paragraph 0083). Thus, Pennica does not support the asserted diagnostic utility. Moreover, Pennica suggests WISP-2 functions as a tumor suppressor. Pennica at 14722. In cancers where WISP-2 is acting a tumor suppressor patients exhibiting enhanced CTGF-3 gene expression would not be expected to experience a worse clinical outcome relative to patients expressing the gene at a lower level. Thus, Pennica does not support the asserted prognostic and therapeutic utilities.

Saxena (Mol Cell Biochem. 2001 Dec;228(1-2):99-104) has been considered. Saxena used various breast tumor cell lines to show WISP-2 expression. However, Botstein (WO

99/21998) shows that expression of human WISP-2 RNA is negative in benign and malignant breast epithelial cells and that expression of WISP-2 is not specific to cancer, as indicated above. Therefore, the results of in vitro studies with breast cancer cell lines are not predictive of results with benign and malignant breast epithelial cells in human tumor tissue samples. Furthermore, Saxena indicates that the role of WISP-2 expression is uncertain and debatable (page 103, left column, last full paragraph).

Zoubine (Biochem Biophys Res Commun. 2001 Mar 30;282(2):421-5) has been considered. However, Zoubine, like Saxena, studies WISP-2 expression in a breast cancer cell line, and the results of in vitro studies with breast cancer cell lines are not predictive of results with benign and malignant breast epithelial cells in human tumor tissue samples, as indicated above. Further, Zoubine indicates that a role for WISP-2 during tumorigenesis is suspected but remains unproven (Abstract) and that the primary modular architecture of WISP-2 is distinctly different from other known members of the WISP sub-family. The domain structure of WISP-2 suggests its function in normal physiological and pathophysiological process may be different from that of WISP-1 and WISP-3. Page 421, paragraph bridging left and right columns. WISP-2 expression studies are inconsistent (page 421, right column, last full paragraph). The functional significance of WISP-2 has not yet been established (paragraph bridging pages 423-424). Considering the possible complexity of WISP-2 function in different tumors, it seems logical to assume that it may not be a universal positive regulator of cell proliferation (paragraph bridging pages 424-425). Saxena and Zoubine, taken with Botstein (WO 99/21998) and Pennica, do not support applicants' asserted utility of CTGF-3 in the diagnosis, prognosis, and/or treatment of cancer.

Inadera (Biochem Biophys Res Commun. 2000 Aug 18;275(1):108-14) and Inadera (Biochem Biophys Res Commun. 2002 Jun 14;294(3):602-8) have been considered. However, Inadera, like Zoubine and Saxena, studies WISP-2 expression in a breast cancer cell line. However, Botstein (WO 99/21998) shows that expression of human WISP-2 RNA is negative in benign and malignant breast epithelial cells and that expression of WISP-2 is not specific to cancer, as discussed above. Therefore, the results of in vitro studies with breast cancer cell lines are not predictive of results with benign and malignant breast epithelial cells in human tumor tissue samples, as indicated above. Furthermore, the present specification does not provide any evidence regarding the estrogen- or Wnt-1-responsiveness of CTGF-3. The present specification does not disclose anything regarding screening environmental compounds for estrogenicity via CTGF-3 induction. Furthermore, Inadera (2000) discloses that the rat ortholog, rCop-1, was identified as a gene whose expression became lost after cell transformation; transfection of rCop-1 into transformed cells suppressed their growth and this was attributed to cell death rather than growth arrest (page 113, paragraph bridging left and right columns). In contrast to the present specification teaching that patients exhibiting enhanced connective tissue growth factor-3 gene expression will experience a worse clinical outcome relative to patients expressing the gene at a lower level, Inadera (2000) appears to suggest that the tumor suppressive properties of WISP-2 may predict a better clinical outcome in breast cancer ((page 113, paragraph bridging left and right columns, last sentence). Inadera (2000) and Inadera (2002), taken with Botstein (WO 99/21998) and Pennica, do not support applicants' asserted utility of CTGF-3 in the diagnosis, prognosis, and/or treatment of cancer.

Grotendorst (2005) discloses that CTGF is capable of stimulating cell proliferation or cellular differentiation depending on other environmental conditions, such as the presence or absence of other growth factors and cytokines (paragraph bridging pages 729-730). Specifically, The N-terminal domain of CTGF mediates differentiation and collagen synthesis in concert with IGF-2; the C-terminal domain of CTGF mediates cell proliferation in concert with EGF (page 730, left column, full paragraph 1). Although Grotendorst indicates that the high degree of sequence conservation in the various CCN family members suggests a commonality of function in these different gene products (page 731, paragraph bridging left and right columns), Grotendorst also proposes that other CCN family members may function as antagonists to CTGF or some other CCN family member, and that further experimentation will be required to elucidate these possibilities (paragraph bridging pages 736-737). An antagonist of CTGF or some other CCN family member does not support the diagnosis, prognosis, and/or treatment of connective tissue-related diseases such as fibrosis and fibrotic conditions in the manner disclosed in the present specification.

Leask (J Cell Sci. 2006 Dec 1;119(Pt 23):4803-10) discloses that CCN expression is reduced in cancers (page 4807, left column, full paragraph 1), which is opposite to what the present specification believes regarding the expression of CTGF-3 in cancer (paragraph [0083]. Although Leask discloses that TGF-β also induces CCN1, CCN4 and CCN5, but not CCN6, and reduces CCN3 expression; data obtained regarding the control of CCN2 gene expression by TGF-β are therefore likely to be applicable for CCN1, CCN4 and CCN5 (page 4807, paragraph bridging left and right columns), the examiner can find no evidence that CCN5 is "overexpressed in pathological conditions that affect connective tissues, including scarring, fibrosis and cancer."

As indicated previously, Grotendorst proposes that other CCN family members may function as antagonists to CTGF or some other CCN family member. Therefore, Leask in view of Grotendorst does not support the diagnosis, prognosis, and/or treatment of connective tissue-related diseases such as fibrosis and fibrotic conditions in the manner disclosed in the present specification.

Moreover, each of WO 98/58063, WO 99/14327, WO 99/21998, Pennica, Saxena, Zoubine, Inadera (2000), Inadera (2002), Grotendorst (2005), and Leask describe experimental results obtained after the filing of the application. The conclusions drawn from these experiments do not reflect knowledge or establish facts available as of the application filing date of the present application. Furthermore, these post-filing date publications do not corroborate the specification's assertion of utility, as discussed above. These post-filing date publications are not evidence of what would be considered credible by a person of ordinary skill in the art at the time of applicants' invention and are not evidence those of skill in the art would have recognized the asserted utilities as well-established. Here, the post-filing publications support the Examiner's position that the invention is not useful in its current form, but requires further research. The asserted utilities of the claimed polynucleotides would require or constitute carrying out further research to identify or reasonably confirm a "real world" context because at the time of filing most of the members of the CCN family lacked a clear biological activity and the development of biological assays for these molecules is problematic (Grotendorst (Cytokine Growth Factor Rev. 8:171-9 (1997), page 172, paragraph bridging columns 1-2 and page 174, column 1, full paragraph 1). Regarding the requirement for further experimentation as a basis for lack of utility, utilities that require or constitute carrying out further research to identify or

reasonably confirm a "real world" context of use are not substantial utilities (M.P.E.P. § 2107.01 I).

Claims 24–39 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that:

> For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, as well as the art cited therein, Applicants assert that the claimed invention complies with the current case law and is supported by a specific, substantial and credible utility as well. The Examiner "should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility' basis unless a 35 U.S.C. 101 rejection is proper." M.P.E.P. § 2107.01 (IV) at 2100-27. Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101

rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY NICKOL, CAN BE REACHED ON (571)272-0835.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID ROMEO/
PRIMARY EXAMINER
Art Unit 1647

DSR
JUNE 25, 2007